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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,118	11/03/2005	Takashi Shinohara	239188	1727

23460 7590 12/05/2008

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EXAMINER
TON, THAIAN N

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
12/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,118	SHINOHARA ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 8/22/08 has been considered. Claim 1 has been amended; claims 12-27 are cancelled; claims 1-11 are pending and under current examination.

This action is non-final.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-12) in the reply filed on 2/6/08 is acknowledged. The requirement is still deemed proper and is therefore made FINAL.

Claims 13-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 2/6/08.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of growing *mammalian* spermatogonial stem cells comprising growing *mammalian* spermatogonial stem cells for at least 3-4 week using a medium containing GDNF, LIF, *EGF and bFGF and serum* does not reasonably provide enablement for methods for growing (1) spermatogonial stem cells from any species; (2) using a medium containing only GDNF and LIF, absent any other

growth factors or serum; (3) using an equivalent of GDNF to culture the spermatogonial stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention. The claimed invention is directed to a method of growing spermatogonial stem cells by culturing the cells for at least 3-4 weeks using a medium containing GDNF, an equivalent thereof and LIF. Further embodiments are directed to growth factors and serum that may be present in the medium.

Breadth of the claims. The breadth of the claims are directed to 1) spermatogonial stem cells isolated from any animal species 2) medium that only has GDNF and LIF and does not include any growth factors or serum; and 3) using an equivalent of GDNF and LIF to culture the spermatogonial stem cells.

Guidance of the Specification/The Existence of Working Examples. The specification teaches methods of isolating mouse spermatogonial stem cells (Example 1); the specification teaches the *in vitro* culture of mouse spermatogonial stem cells using a medium containing GDNF, bFGF, EGF, LIF and FCS. The specification teaches that GDNF is known to stimulate spermatogonial self-renewal *in vivo* and that the other factors affect the proliferation and maintenance of other stem cells, including primordial germ cells. The specification teaches that cells were cultures and transferred between 10-14 days, and that by 3-4 weeks, the cultures remained in a steady state and that the cells resembled mitotic spermatogonia. The specification teaches that the combination of GDNF, bFGF,

EGF, LIF were shown to increase in spermatogonial having potential for stem cells *n vitro*. The cells were then evaluated *in vitro* (p. 36) and *in vivo* (p. 37). The specification teaches that the cells were transplanted into infertile mice and found that the mice produced normal spermatogenic cells that were capable of being used to produce pups (pp. 39-40). The specification further teaches the generation of transgenic spermatogonial stem cells and production of a transgenic animal by transplanting the stem cells (pp. 42-43, Example 2).

State of the Art/Predictability of the Art. The state of the art of culturing mammalian stem cells is not predictable with respect to the particular factors and conditions that would be used in order to culture spermatogonial stem cells. In particular, Applicants' Remarks, filed 8/22/08, allude to this fact by stating that the instant specification discloses that after culturing spermatogonial stem cells for 3-4 weeks, under specific conditions, including GDNF, LIF, bFGF and EGF, other spermatogonial cells may die, but spermatogonial stem cells grow to form stable colonies and can be further passaged for several months. See page 7, 3rd ¶ of the Response. In particular, Applicants' Remarks state that the Creemers reference (cited previously) does not disclose culturing spermatogonial stem cells for 3-4 weeks, showing that their culture period of 7 days showed decreased viability to about 10% (p. 7, 1st ¶ of the Response). Thus, the Creemers reference provides guidance to show that the state of the art of culturing spermatogonial stem cells is not predictable; additionally, the Creemers reference does not teach the same factors (for example, EGF and serum) and only teach that using LIF, bFGF and GDNF, causes high percentages of cell death. The instant specification further supports this observation stating that, "Although spermatogonial stem cells can survive when cultured *in vitro* using one of the above-described methods (*i.e.*, art-recognized culture conditions) of cultivation, the number of cells decreases to about 20% of the original number in 1 week under the present situation, and it is impossible to grow the cells." See p. 4, lines 10-15. Similarly, the specification

teaches that there have been no successful attempts to grow spermatogonial stem cells *in vitro* to the extent that permits practical application of them (p. 3, lines 22-24, p. 22, lines 1-11). Particularly, the specification teaches GDNF stimulates spermatogonial stem cell self-renewal *in vitro* and that bFGF, EGF, LIF and FCS affect proliferation and maintenance of other stem cells (p. 34, lines 19-22), and that the combination of these factors, along with culture for at least 3-4 weeks results in a reproducible method of growing spermatogonial stem cells. Accordingly, the scope of enablement has been limited to the particular factors used by the instant invention, to culture spermatogonial stem cells, because the specification provides no guidance to show culturing spermatogonial stem cells in any other conditions to successfully grow spermatogonial stem cells for 3-4 weeks to overcome the art-recognized unpredictability in the viability of the cells. Additionally, the claims recite utilizing an equivalent of GDNF for culturing the cells (see lines 3-4 of the instant claims). The claims have been limited to GDNF, because the specification, although contemplating utilizing GDNF-like compounds, provides no guidance for utilization of the breadth of these compounds for methods of growing spermatogonial stem cells, as instantly claimed. Additionally, the specification contemplates a broad range of compounds, as well as factors that exhibit an action similar to GDNF (p. 13, lines 22-34). There is no guidance as to what factors would have actions that are similar and would result in growing spermatogonial stem cells for 3-4, such that using these equivalents of GDNF would overcome the art-recognize unpredictability of viability in culturing spermatogonial stem cells.

Additionally, the claims are limited to the scope of mammalian spermatogonial stem cells, because the specification provides specific guidance for culturing mouse spermatogonial stem cells, however, the specification does not provide any guidance for any factor(s) that would be equivalently used for other species of animals, for the breadth claimed. For example, the specification does not teach the factors necessary to culture avian, or various types of insect

spermatogonial stem cells; the specification does not provide any guidance for the equivalent of LIF, or GDNF in these species such that one of skill in the art could predictably culture spermatogonial stem cells from species other than mammal. In particular, the state of the art of spermatogonial stem cells is such that one of art would reasonably predict that GDNF, LIF, EGF, bFGF and serum to effectively grow mammalian spermatogonial stem cells because Ryu *et al.* (**PNAS**, 102(40): 14302-14307, October 2005) show that self-renewal of spermatogonial stem cells (SSCs) between rats and mice are identical, and suggest a conservation of the signaling factors for SSCs (Abstract). Ryu further states that, "The dependence of rat SSCs on GDNF, GFRα1, and bFGF for continuous proliferation in culture is identical to the situation in the mouse and rat and reflects a remarkable similarity in these two species that diverged 12-24 million years ago. Previous studies demonstrated that rat SSCs transplanted to mouse seminiferous tubules generated long-term rat spermatogenesis, indicating a conservation of stem cell self-renewal factors, as well as germ cell differentiation factors, between the two species. Moreover, SSCs from a wide range of species, including rabbit, pig, baboon, and human, that have diverged from the mouse 50-100 MYA will replicate after transplantation to mouse seminiferous tubules. Thus, the self-renewal signaling pathway for these stem cells is also likely to have been conserved and be the same as those identified for the mouse and rat. However, in these more distantly related species, germ cell differentiation factors are not conserved, because stem cells replicate after transplantation to the mouse, but germ cell differentiation and spermatogenesis do not occur." See p. 14306, col. 2, 1st full ¶.

The Amount of Experimentation Necessary. Accordingly, in view of the unpredictable state of the art of culturing spermatogonial stem cells, with regard to the viability of *in vitro* cultured SSCs, the lack of guidance or teachings provided by the specification for culture conditions of SSCs for 3-4 weeks, other than the exemplified conditions which require GDNF, LIF, bFGF, EGF and serum, the state

of the art of SSCs which suggests that mammalian species would likely require the same factors for stem cell self-renewal, but more distantly related species (for example, insects or birds) may not have these factors conserved, it would have required undue experimentation for the skilled artisan to make and use the full breadth of the claimed methods.

Claim Rejections - 35 USC § 102

The following rejections have been **withdrawn** in view of Applicants' cancellation of claim 12:

1) Claim 12 under 35 U.S.C. 102(a) as being anticipated by Nagano *et al.* (2003).
2) Claim 12 under 35 U.S.C. 102(b) as being anticipated by Nagano *et al.* (1998)
3) Claim 12 under 35 U.S.C. 102(b) as being anticipated by Nagano *et al.* (2001).

The prior rejection of claims 1-3, 5, 6 and 12 under 35 U.S.C. 102(b) as being anticipated by Creemers *et al.* is withdrawn in view of Applicants' arguments and amendment to the claims, which now require culturing the stem cells for at least 3-4 weeks.

Claim Rejections - 35 USC § 103

The following rejections are **withdrawn** in view of Applicants' remarks and amendment to the claims:

1. Claims 1-7, 9, 11, 12 under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.,* as evidenced by Human embryology, Embryogenesis when taken with Nagano *et al.* (2003)

2. Claims 1-3, 5-9 and 12 under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.* (above) as evidenced by Human embryology, Embryogenesis (above) when taken with Wahab-Wahlgren in further view of Haneji *et al.*.

3. Claims 1-3, 5-7, 9, 10 and 12 under 35 U.S.C. 103(a) as being unpatentable over Creemers *et al.* (above) as evidenced by Human embryology, Embryogenesis (above) when taken with Izadyar *et al.*

In particular, Applicants' amendment to the claims now requires that the cells are cultured for at least 3-4 weeks; additionally, Applicants' arguments are found to be persuasive with respect to Creemers teaching that after 7 days of culture, it is found that only 10% of SSCs survive, and that there would have been no reason to culture SSCs for 3-4 weeks as required by the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632